Organophosphate-Modulated Cardiac Membrane Currents: Computer Study of the Genesis of LQTS

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Abstract

An important clinical marker of organophosphate (OP)–caused cardiac toxicity is long-QT syndrome (LQTS), the elongation of the repolarization period in the ventricles, as measured in an electrocardiogram (ECG). The primary membrane currents responsible for this condition are two potassium currents, i_{Kr} and i_{Ks}. This computer simulation investigated the effect of the modulation of the cardiac membrane currents on the action potential in a two-dimensional slab of tissue affected by OP. We have shown that modulation of the sodium current and reduction of the potassium currents mimic the experimentally observed change in slope of the depolarization in the presence of organophosphates as well as the prolongation and shape of repolarization, a precursor to the onset of Torsade de Pointes (TdP) and ventricular fibrillation (VF).

1. Introduction

Organophosphorous compounds cause repolarization abnormalities of the ventricles, a precursor to the often-fatal cardiac arrhythmia.

An important clinical manifestation of OP-caused cardiac toxicity is the appearance of LQTS, refs. [1-3]. This condition has also been tied to mutations in several genes, including HERG, and encoding ion channels and can also be induced by medication (acquired LQTS). The result is modulated ion flow, a reduced potassium outflow; but an inflow of excess sodium does not appear to take place. It may also be tied in to the overshoot potential of chloride. The calcium ion distributions within the cells are also altered. A delayed influx of Ca^{++} ions contributes to early-after depolarization (EAD), thought to trigger ventricular arrhythmias.

Kiss and Fazekas [4], Ludomirsky et al. [5] and Bar-Meir et al. [6] discuss clinical cases of OP-affected individuals that often progress from bradycardia, at the onset of the poisoning, to TdP that may culminate in ventricular fibrillation and sudden cardiac death (SCD). With OPs, there is often a delay of up to 2 weeks, the intermediate stage before the VF fully manifests itself.

The effect of OP on the cardium is expressed in an overload of ACh, lesions in the tissue and blockage of the second messenger system, VIP. Table I summarizes the most important effects on the heart. For additional information, see refs. [7-9].

Animal models and experimental data show that in OP-caused poisoning, the slope of the onset of the depolarization governed by the influx of the Na^+ ions is changed. In addition, modulation of the potassium currents, i_{Kr} and i_{Ks}, are observed. Plateau current imbalance and a blockage of the ion channel responsible for these currents are thought to play a role. Under these circumstances, a prolongation of the repolarization time of the ventricles results. A repolarization lengthening by a few percent is an indicator of a precursor to arrhythmogenicity. Action-potential duration (APD) lengthening enables (EADs), triggering focal arrhythmia.

Zeng et al. [10], working with guinea pig ventricular myocytes found that i_{Ks} is the major plateau repolarization current and block of either i_{Kr} or i_{Ks} results in abnormal repolarization. Viswanathan et al. [11] showed that the effect of the heterogeneity of i_{Ks} and i_{Kr} has a profound influence on APD and may influence arrhythmogenesis. Differences in cardiac cell types contribute to this heterogeneity. Liu et al. [12] found that smaller i_{Ks} prolongs the action potential of the midmyocardial myocytes.

The following sections describe a computer study of the effect of OP presence on the electrophysiology of ventricular tissue, especially the processes, through reentry, leading to conditions favorable to VF.

2. Methods and materials

The dynamics and integrity of the action potential propagation in 3 cm x 3 cm ventricular tissue, whose electrophysiological behavior is described by the Luo and Rudy model [13], was studied. For the computations, the tissue was represented as a slab of 300 x 300 x 1 nodes. The stimulus was applied to the left-hand

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Table I. Effect of OPs on Cardiac Tissue

Bound to AChE	Lesions				Second Messenger (VIP, others)
	Acidosis	Anoxia	Modulated Ion Concentration	Release of Catecholamines	
ACh overload causes bradycardia, slows conduction in AV Prevents hydrolysis $[Ca^{+2}] \uparrow \rightarrow I_{KACh} \uparrow$ Antagonizes adenylyl cyclase Arrests cAMP synthesis Depresses I_f (pacemaker current, Na^+, K^+) ACh inhibits adenylate cyclase	(intracellular proton accumulation), pH $\downarrow$, Na^+/H^+ exchange $\uparrow$ [ATP] $\downarrow$ $[K^+]_o \uparrow$, reduces I_{Kr} by increasing rate of deactivation, shifts voltage dependence of activation to more positive potentials $g_K \uparrow$ Cytoplasmic $[Ca^{2+}] \uparrow$ slows repolarization, reduces max diastolic potential $I_{Ca(L)} \downarrow$ $I_{Na} \downarrow$ (inactivation of fast Na^+ channel) Decreased excitability CO_2 accumulation	Lowers ATP, cAMP, cGMP, ATPase inhibition $I_{K(ATP)} \uparrow$ (activated), AP shortened	$[K^+]_o \uparrow$ Effect on velocity of propagation, inexcitability $[Na^+] \uparrow$ Na^+/K^+ pump inhibition Na^+/Ca^{2+} exchanger $\rightarrow$ Ca^{2+} influx $[Ca^{2+}] \uparrow$ Na^+/Ca^{2+} exchanger $\downarrow$ reduced SR uptake $[Mg^{2+}] \uparrow$ (hydrolysis of ATP), activates enzymes Reduces $I_{Ca(L)}$, I_{K1}, I_{KACh}, $I_{K(ATP)}$, I_{Ks}	Prolongs AP, $[Na^+] \uparrow$, Na^+ - K^+ ATPase antagonized DAD enhanced Difference for α, β receptors α stimulation: reperfusion arrhythmia (Ca^{2+} overload), gap junction conductance $\downarrow$, exchanger stimulation, activates Na^+/K^+ pump β stimulation: stimulate adenylate cyclase, elevate cAMP, increase Ca^{2+} influx, I_f activation, triggered activity improves modal conduction	Adenylate cyclase activation $I_f \uparrow$, cAMP $\uparrow$, $\rightarrow$ HR $\uparrow$ OP reduces cAMP $\rightarrow$ Ca^{2+} influx, inhibitsadenylate cyclase, stimulates ATP , $I_K \uparrow$ affects $I_{Ca(L)}$, EAD, DAD $\rightarrow$ arrhythmia
Intermediate Stage					
AF, VF					

Notes: g represents conductivity of the tissue; [..] indicates concentration; $I_{(.)}$ means ionic current with the subscript denoting the channel type; $\uparrow$ is an increase; $\downarrow$ is a decrease; $\rightarrow$ means yields.

edge and consisted of a pulse of 200 $\mu A/cm^2$ of 2 ms in duration. The presence of OPs was modeled by modifying the conductivity of the channels thought to be affected. This is coarse graining the problem since localized sodium and calcium concentration deviations due to OP presence are also indicators of the change of the state. In addition to modulating the potassium current, OP-caused lesions in the tissue were modeled by including the effect of anoxia, simulated by modulation of calcium conductivity, and acidosis by a reduction of calcium and sodium conductivities. Pacing was used to ensure stable initial conditions.

3. Computational approach

For the calculations reported here, a monodomain approach was adopted with fiber orientation (one of the diffusion matrix entries) assumed to be uniform. The propagation of the action potential was based on the following cable equation:

$$\frac{\partial V}{\partial t} = -I_{ion}/C_m + D\left(\frac{\partial^2 V}{\partial x^2} + \frac{\partial^2 V}{\partial y^2}\right)$$

In this equation, V is the membrane voltage and I_{ion} the transmembrane ionic current, mainly made up from the sodium, potassium, calcium and chloride currents, and pumps and exchangers. D is the diffusion constant and C_m the membrane capacitance. Appended are the gating variables of the ionic channels and equations for the change of the ion concentrations. No flux boundary conditions were used. After determining the baseline in these simulations, the approach was to vary the ion channel conductivities thought to be affected in OP-affected tissue. Specifically, the potassium conductivities were lowered to one-tenth the normal value. The sodium conductivity was lowered from 16 to 1.6 S/cm^2. The effect of the change of the background current and the calcium concentration was studied separately.

The calculations were carried out with the code CardioWave on the computer assets of the Major Shared Resource Center (MSRC) at Aberdeen Proving Ground, MD.

In parallel mode, a typical calculation on 16 nodes of the Origin 3000, with 300-MHz IP27 processors and data cache size of 32 kbytes, required 7 hr and 15 min of non-dedicated time. This time was improved with a larger number of processors, but the speedup was not linear.

4. Results

In this model, the baseline cycle length was 400 ms. The conduction velocity was around 60 cm/s. The plateau, representing the repolarization, extended from 50 ms to 300 ms, followed by a steep decline to the resting voltage of –84 mV. Changing the potassium channel conductivities to one-tenth the normal value resulted in considerable cycle lengthening, (see Fig. 1). Increasing the slow inward calcium current by doubling the channel conductivity more than doubled the peak of the potential voltage and extended the cycle time by several hundred milliseconds. Decreasing the background current by adjusting the conductivity to one-tenth the normal value had two effects: the maximum value of the depolarized voltage approached 50 mV, and the cycle lengthened to 500 ms (see Fig. 2). The repolarization plateau showed a gradual decline, with a precipitous drop from –25 mV to –84 mV commencing at 450 ms into the cycle. When the background conductivity was doubled, the action potential oscillated in the negative voltage range, reaching only –20 mV. Cycle lengthening was also observed when the g_{K1} was lowered to 0.1; indeed, a 25% increase was noted.

Finally, reentry was observed when a second stimulus, perpendicular to the initial one, was launched at 425 ms (Figs. 3 and 4). It should be noted that the second wave propagated transversally much faster in portions of the tissue that had longer to recover. The characteristic spiral presaging reentry was observed at the head of the wave front.

5. Discussion

Animal experimental data show that OP intoxication results in lesions of the cardiac tissue, acidosis, and anoxia. These effects in terms of the membrane currents can be expressed and simulated by ion channel conductivity changes. Potassium conductivity changes, which can be caused by ligand blocking the channel, are a major contributor to increased cycle length and consequently LQTS. Modulating the channels that are affected by OP, LQTS can be simulated. It is clear that this is a precursor to reentry and the onset of fibrillation. This also suggests possible new approaches (see ref. [14], for example) to the prevention and treatment of OP toxicity. Planned experiments in the near future should help to validate this approach.

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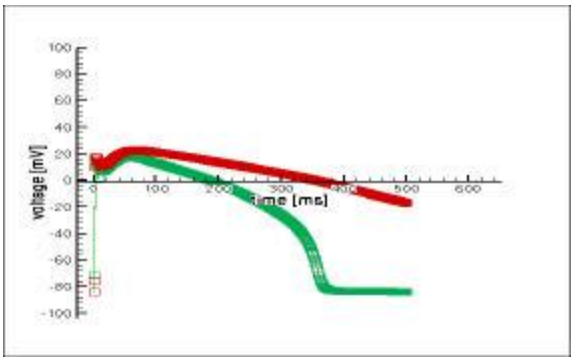

Figure 1. The baseline (lower) contrasted with the reduction in potassium channel conductivity (upper).

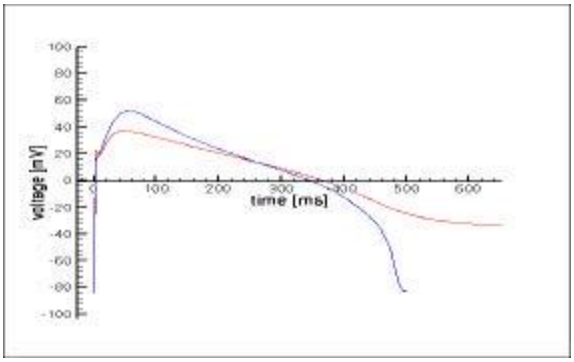

Figure 2 The effect of lowering the background current (lower) and increasing the inward Ca^{++} ion flow.

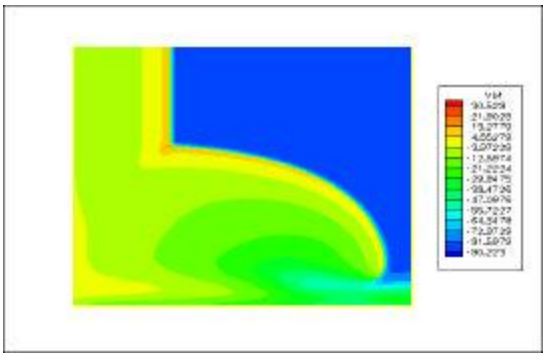

Figure 3. The effect of the interaction of two waves running perpendicularly, with the second started at 425 ms.

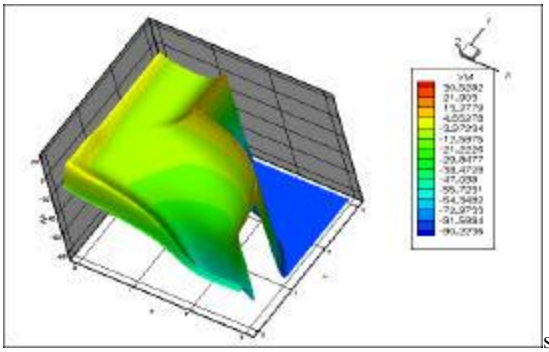

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Figure 4. The incipient generation of reentry upon the start of the second wave.